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IL-4/13 Blockade and sleep-related adverse drug reactions in over 37,000 Dupilumab reports from the World Health Organization Individual Case Safety reporting pharmacovigilance database (VigiBase™): a big data and machine learning analysis

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Abstract. – OBJECTIVE: Atopic dermatitis displays a relevant sleep burden sustained by clinical (i.e., itch), psychological (i.e., inadequate coping strategies) and therapeutic (i.e., frequent loss of drug response) triggers. Dupilumab, the first biologic approved for atopic dermatitis, showed excellent effects on improving pruritus and sleep after only two weeks of treatment but, in some cases, may have paradoxical effects. The rate of sleep-related side-effects remains unknown. More specifically, adverse-drug reactions (ADRs) related to dupilumab have been investigated during the safety phase of randomized clinical trials or in small retrospective epidemiological surveys, but little is known about sleep-related ADRs in real-life settings. Therefore, we took advantage of a global large-scale pharmacovigilance database, carrying out a comprehensive data mining analysis to look at different sleep-related ADRs reported among patients under anti IL-4/13 therapy.

MATERIALS AND METHODS: We analyzed individual case study reports (ICSRs) in VigiBase™, the World Health Organization (WHO) global pharmacovigilance database of ADRs collected by national drug authorities in > 140 countries (> 90% of the world population). We looked for patterns of potentially sleep-related ADRs and we applied a disproportionality analysis based on Bayesian Confidence Propagation Neural Network (BCPNN). A meta-analytical approach was used to synthesize the overall effect size of sleep-related ADRs potentially associated to Dupilumab administration.

RESULTS: From inception up to March 9, 2021, 94,065 ADRs from 37,848 unique reports were

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included and analyzed in the present paper: 1,294 of them (1.4%) concerned sleep disturbances (n=27). Most of sleep-related complaints were generic sleep disorders (n=630), followed by insomnia (n=312), somnolence (n=81), lethargy (n=60), night sweats (n=30), middle insomnia (n=39), hypersomnia (n=25), poor-quality sleep (n=21), initial insomnia (n=17), sleep apnea syndrome (n=13), nightmares (n=11) and sleep deficit (n=11). Interestingly, restlessness and restless leg syndrome, nocturnal dyspnea, narcolepsy and bruxism were reported in 7, 6, 5, 4 and 3 cases, respectively. Only sleep deficit [OR 15.67 (95% CrI 8.61-28.51); IC 3.24 (95% CrI 2.26-3.97)], generic sleep disorder [OR 6.22 (95% CrI 5.74-6.73); IC 2.60 (95% CrI 2.48-2.71)], nocturnal dyspnea [OR 3.68 (95% CrI 1.53-8.87); IC 1.56 (95% CrI 0.03-2.56)] and middle insomnia [OR 1.87 (95% CrI 1.36-2.56); IC 0.88 (95% CrI 0.39-1.30)] achieved the statistical significance threshold.

CONCLUSIONS: In this work, we identified over 37,000 unique case-reports of Dupilumab side-effects reported on the WHO pharmacovigilance database. We specifically categorized those related to sleep issues, which were 1,294. Our findings from large numbers of cases provide data supporting the clinical observations that Dupilumab is usually effective in improving sleep quality and sleep disturbances/impairments, given the lack of statistical significance of several sleep-related ADRs. Further work is needed to closely scrutinize the impact of Dupilumab on sleep, in terms of underlying mechanisms, and to better understand residual sleep disorders in patients with atopic dermatitis and other allergic diseases treated with Dupilumab. Thus, sleep monitoring may be helpful for dermatologists in managing atopic dermatitis patients treated with dupilumab. The limitations of spontaneous reporting systems including underreporting and reporting bias, heterogeneity of sources and impossibility to infer any causal relationship merit consideration and further research is needed.

Key Words:
Dupilumab, Pharmacoepidemiology, Pharmacovigilance, Adverse drug reaction, Bayesian Confidence Propagation Neural Network (BCPNN), Sleep disorders.

Introduction

Atopic dermatitis is a commonly diagnosed disease, which affects approximately from 15% to 30% of children and from 2% to 10% of the adult population. It ranks 15th among all nonfatal disorders and has the highest disease burden among all skin diseases in terms of disability-adjusted life-years (DALYs), according to the latest available estimates of the Global Burden of Disease (GBD) 2017 Study[1-3].

Atopic dermatitis is a chronically relapsing pruritic inflammatory skin disorder, the etiopathogenesis of which has still to be fully elucidated. Mechanisms underlying its multi-factorial, complex, nonlinear pathophysiology include alterations, dysfunctions, and dysregulations of the epithelial barrier, the interplay of environmental stimuli and triggers, and the role of unhealthy lifestyles, like alcohol uptake and smoking, among others[4-6].

Atopic dermatitis exerts a detrimental impact on quality of life, imposing a relevant psychological and clinical burden, due to several autoimmune and metabolic co-morbidities. Furthermore, patients with atopic dermatitis usually complain of sleep disturbance, which is, indeed, rather common and has been consistently found to dramatically impact health-related quality of life[7]. Poor sleep/sleep disturbance can be considered as one of the symptoms of the clinical manifestation of atopic dermatitis, together with pain and itch (the so-called "triad of atopic dermatitis"). When quantitatively assessing the severity of this disease, dermatologists commonly utilize the "Eczema Area and Severity Index" and the SCORAD index, which are composite scoring indexes that include the measurement of subjectively reported sleep loss[7]. Sleep disturbance is one of the patient-reported outcome measures (PROMs) which are being increasingly collected by epidemiological surveys, as well as by clinical trials aimed at investigating if a certain drug can improve sleep quality[8].

The relationship between sleep disturbance and atopic dermatitis is particularly complex and many dermatologists have shifted from considering it as just one of the symptoms clinically observable or a proxy of its disease to considering it as one of the possible co-morbidities of atopic dermatitis, with its own clinical dignity[2]. This paradigmatic shift warrants further research in the area and studies specifically designed to dissect the nature, mechanisms, and determinants of the relationship between sleep impairment and atopic dermatitis.

In the available scholarly literature, a variety of sleep disorders, either subjectively or objectively associated with atopic dermatitis, are reported, imposing highly heterogeneous effects and impacts among patients with atopic derma-

titis[2]. Recent evidence seems to suggest that the association between sleep disorders and atopic dermatitis might be bidirectional and polycausal rather than unidirectional, potentially forming a "vicious cycle", with atopic dermatitis leading to the insurgence of sleep issues and these, in their turn, worsening the clinical history of atopic dermatitis (both in terms of severity and prognosis)[2]. Recently, Chang and Chiang[2] have critically reappraised existing literature and have proposed considering sleep disorders as a comorbidity of atopic dermatitis for which regular and specific screening and treatment should be implemented, utilizing a holistic, comprehensive management approach. As such, strategies targeting sleep quality are expected to better control atopic dermatitis and improve patient's health-related quality of life as a whole[2].

Atopic dermatitis is quite commonly the first manifestation of a broader "atopic diathesis", which includes asthma and allergic rhinitis, and which can affect genetically predisposed subjects[9]. Up to 80% of children suffering from atopic dermatitis can later develop asthma or allergic rhinitis[9,10].

Sleep disorders represent an important issue also in these two conditions[11-13]. For instance, according to the "Prevention and Incidence of Asthma and Mite Allergy" (PIAMA) birth cohort study, children with frequent asthma symptoms were found to have a higher likelihood of reporting excessive daytime sleepiness[14]. A study[12] that enrolled 591 patients with rhinitis found that all the dimensions of sleep were impaired by this allergic disease, in particular in the severe type when compared to the mild one. However, the duration of allergic rhinitis (that is to say, intermittent or persistent) had no impact on sleep quality[12].

Dupilumab (brand name Dupixent®, produced and sold by Sanofi and Regeneron) is a fully human monoclonal antibody, binding IL-4 receptor alpha (IL-4Rα) and thus inhibiting the signaling pathways of IL-4 and IL-13. Due to its unique blockade properties, it is utilized for the treatment and management of patients suffering from allergic diseases, including eczema/moderate-to-severe atopic dermatitis, as well as for asthma and nasal polyps resulting in chronic sinusitis. Commonly reported side-effects include allergic reactions, cold sores, and ocular reactions, such as inflammation of the cornea, among others[15,16].

Side-effects and adverse-drug reactions (ADRs) related to dupilumab have been investigated during the safety phase of randomized clinical trials or in small retrospective epidemiological surveys[17,18], but little is known about sleep-related ADRs in real-life settings. Therefore, we took advantage of a global large-scale pharmacovigilance database, carrying out a comprehensive data mining analysis to look at different sleep-related ADRs reported among patients under anti IL-4/13 therapy.

Materials and Methods

Database

VigiBase™ is the global pharmacovigilance database devised and curated by the Swedish World Health Organization (WHO) Collaborating Centre for International Drug Monitoring, named as the Uppsala Monitoring Centre (UMC), The database was searched from inception up to March 9, 2021. UMC collates more than 20 million individual case safety reports (ICSRs) of suspected adverse drug reactions (ADRs), collected from more than 140 countries, members of the WHO Program for International Drug Monitoring.

Disproportionality Analysis

To quantitatively investigate the association between the drug and the suspected ADR, several disproportionality measures between the observed and the expected reporting of a medicine-ADR pair can be computed, like odds-ratio (OR) and the information component (IC). The latter was initially devised and implemented through the Bayesian Confidence Propagation Neural Network (BCPNN): if IC is a positive (or negative) value, the pair under study is reported more often (or less frequently) than expected, based on all the reports included in VigiBase™.

$$IC = \left(\frac{N_{observed} + 0.5}{N_{expected} + 0.5} \right)$$

where

$$N_{expected} = \frac{N_{drug} \cdot N_{reaction}}{N_{total}}$$

$N_{expected}$ is the number of case reports expected for the given drug-effect pairwise association, $N_{observed}$ is the actual number of case reports for the drug-ADR combination under study. N_{drug} is

the number of all case reports for the medicine under scrutiny, regardless of the effects reported, and, conversely, $N_{reaction}$ is the number of case reports for the given side-effect under study, regardless of the specific type of drug.

All these disproportionality measures are calculated with their 95% credible interval (CrI), with $IC_{0.25}$ and $IC_{97.5}$ being the lower- and upper-bound values, respectively.

In the current study we reported both OR and IC. Interpretation of the IC is as follows: IC is statistically significant when its lower-bound ($IC_{0.25}$) is greater than zero. We reported both disproportionality measures because, if on the one hand OR is usually employed in biomedicine, IC, relying on data mining approaches, allows to minimize the chance of detecting spurious statistically significance.

ADRs Categorization and Classification

The Medical Dictionary for Drug Regulatory Authorities (MeDRA) ontology at the System Organ Class (SOC) level was utilized to categorize suspected ADRs related to Dupilumab. Sleep-related ADRs were assessed in the present investigation. Finally, an overall effect size (for OR) was computed utilizing meta-analytical tools (Comprehensive Meta-Analysis Software version 3.3.070, Biostat, Englewood, NJ, USA). Funnel plot was inspected to investigate any potential reporting bias.

Results

From inception up to March 9, 2021, 94,065 ADRs from 37,848 unique reports were included and analyzed in the present paper: 1,294 of them (1.4%) concerned sleep disturbances (n=27). Most of sleep-related complaints were categorized as generic sleep disorders (n=630), followed by insomnia (n=312), somnolence (n=81), lethargy (n=60), night sweats (n=30), middle insomnia (n=39), hypersomnia (n=25), poor quality sleep (n=21), initial insomnia (n=17), sleep apnea syndrome (n=13), nightmares (n=11), sleep deficit (n=11) and abnormal dreams (n=8). Interestingly, restlessness and restless leg syndrome, nocturnal dyspnea, narcolepsy and bruxism were reported in 7, 6, 5, 4 and 3 cases, respectively. More details are shown in Table I.

Table I. Sleep-related adverse drug reactions following Dupilumab administration.

Sleep-related adverse drug reactions	Number of reports	Percentage of reports
Abnormal dreams	8	0.6%
Abnormal sleep-related event	1	0.1%
Breathing-related sleep disorder	1	0.1%
Bruxism	3	0.2%
Daydreaming	1	0.1%
Delayed sleep phase	1	0.1%
Hypersomnia	25	1.9%
Initial insomnia	17	1.3%
Insomnia	312	24.1%
Lethargy	60	4.6%
Middle insomnia	39	3.0%
Narcolepsy	4	0.3%
Nightmare	11	0.9%
Night sweats	30	2.3%
Nocturnal dyspnoea	5	0.4%
Poor quality sleep	21	1.6%
Restless legs syndrome	6	0.5%
Restlessness	7	0.5%
Sleep apnoea syndrome	13	1.0%
Sleep deficit	11	0.9%
Sleep disorder	630	48.7%
Sleep disorder due to a general medical condition	3	0.2%
Sleep disorder due to general medical condition, insomnia type	1	0.1%
Sleep terror	1	0.1%
Snoring	1	0.1%
Somnolence	81	6.3%
Terminal insomnia	1	0.1%
Total	1,294	100.0%

Table II. Statistically significant sleep-related adverse drug reaction-Dupilumab associations.

Disease	OR	$OR_{0.25}$	$OR_{97.5}$	IC	$IC_{0.25}$	$IC_{97.5}$
Sleep deficit	15.67	8.61	28.51	3.24	2.26	3.97
Sleep disorder	6.22	5.74	6.73	2.60	2.48	2.71
Nocturnal dyspnoea	3.68	1.53	8.87	1.56	0.03	2.56
Middle insomnia	1.87	1.36	2.56	0.88	0.39	1.30

Only sleep deficit [OR 15.67 (95% CrI 8.61-28.51); IC 3.24 (95% CrI 2.26-3.97)], generic sleep disorder [OR 6.22 (95% CrI 5.74-6.73); IC 2.60 (95% CrI 2.48-2.71)], nocturnal dyspnea [OR 3.68 (95% CrI 1.53-8.87); IC 1.56 (95% CrI 0.03-2.56)] and middle insomnia [OR 1.87 (95% CrI 1.36-2.56); IC 0.88 (95% CrI 0.39-1.30)] achieved the statistical significance threshold. For further details, the reader is referred to Table II. Non-statistically significant sleep-related ADR-Dupilumab associations are reported for completeness in Table III. Delayed sleep phase was borderline significant [OR 9.66 (95% CrI 1.34-69.65); IC 1.31 (95% CrI -2.49 to 2.95)].

The overall effect-size computed for all sleep-related ADRs was 0.78 (95% CrI 0.43-1.42) for OR (Figure 1), with visual inspection of the funnel plot showing no evidence of reporting bias (Figure 2).

Discussion

In this pharmacovigilance study, we identified over 37,000 unique case-reports of Dupilumab side-effects reported on the WHO pharmacovigilance database. We specifically categorized those related to sleep-related issues, which were 1,294 (1.4%). As such, they represent a very small fraction of all reported complaints. Our findings from large numbers of cases provide data supporting the clinical observations that Dupilumab is effective in improving sleep quality and sleep disturbances/impairments. Further work is needed to closely scrutinize the impact of Dupilumab on sleep, in terms of underlying mechanisms, and to better understand residual sleep disorders in patients with atopic dermatitis and other allergic diseases treated with Dupilumab.

Table III. Non statistically significant sleep-related adverse drug reaction-Dupilumab associations.

Disease	OR	$OR_{0.25}$	$OR_{97.5}$	IC	$IC_{0.25}$	$IC_{97.5}$
Abnormal dreams	0.17	0.08	0.34	-2.50	-3.67	-1.67
Abnormal sleep-related event	0.43	0.06	3.04	-0.92	-4.72	0.72
Breathing-related sleep disorder	3.98	0.56	28.40	0.99	-2.80	2.63
Bruxism	0.46	0.15	1.42	-1.01	-3.06	0.18
Daydreaming	0.57	0.08	4.02	-0.60	-4.39	1.04
Delayed sleep phase*	9.66	1.34	69.65	1.31	-2.49	2.95
Hypersomnia	0.73	0.49	1.08	-0.45	-1.07	0.06
Initial insomnia	1.40	0.87	2.25	0.46	-0.30	1.07
Insomnia	0.71	0.63	0.79	-0.50	-0.66	-0.34
Lethargy	0.65	0.50	0.83	-0.62	-1.01	-0.28
Narcolepsy	0.80	0.30	2.13	-0.29	-2.03	0.79
Nightmare	0.17	0.10	0.31	-2.46	-3.44	-1.74
Night sweats	0.77	0.54	1.10	-0.38	-0.94	0.09
Poor quality sleep	0.80	0.52	1.25	-0.31	-1.01	0.26
Restless legs syndrome	0.27	0.12	0.60	-1.81	-3.18	-0.88
Restlessness	0.11	0.05	0.24	-3.06	-4.32	-2.19
Sleep apnoea syndrome	0.69	0.40	1.19	-0.52	-1.41	0.16
Sleep disorder due to a general medical condition	0.96	0.31	2.99	-0.05	-2.10	1.15
Sleep disorder due to general medical condition, insomnia type	0.40	0.06	2.82	-1.01	-4.81	0.63
Sleep terror	0.29	0.04	2.07	-1.39	-5.19	0.25
Snoring	0.26	0.04	1.88	-1.51	-5.31	0.13
Somnolence	0.19	0.15	0.23	-2.39	-2.72	-2.09
Terminal insomnia	0.61	0.09	4.34	-0.51	-4.31	1.13

*: Borderline statistically significant.

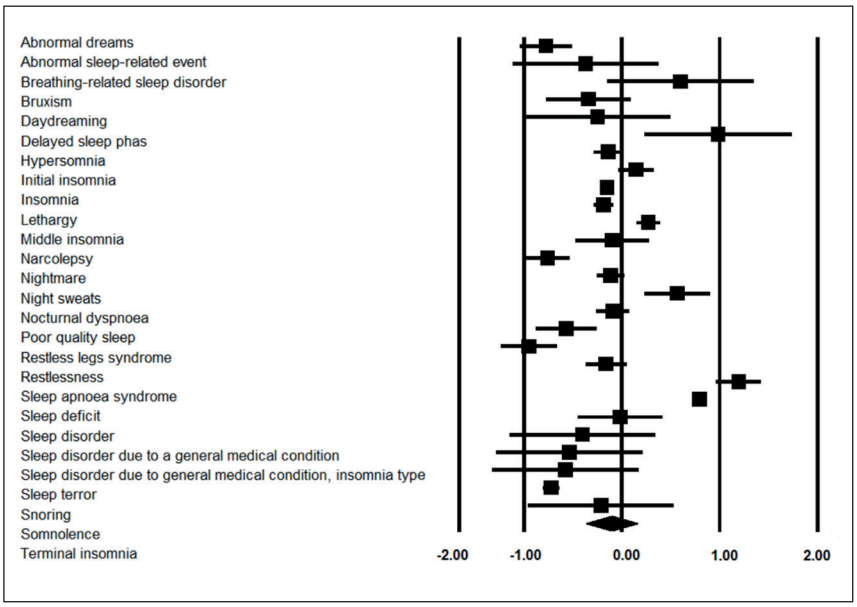

Figure 1. Odds-ratios for all sleep-related adverse drug reaction-Dupilumab associations (on a log-scale).

Dupilumab is used for treating and managing atopic dermatitis, asthma and other related allergic disorders. In the scholarly literature, these diseases have been found to be linked with a variety of sleep issues, including excessive daytime sleepiness which can affect from 43.1% to 61.9% of children with atopic dermatitis. Similarly, adult populations report an OR of 2.66 (95% CI 2.34-3.01) of feeling tired and sleeping during the day[2]. Lower sleep efficiency was reported in 72-76.8% of children, whereas adults were most affected (up to 90.6%)[2]. Insomnia was another sleep issue commonly reported among adults with atopic dermatitis [with an OR of 2.36 (95% CI 2.11-2.64)][2]. Finally, concerning sleep-disordered breathing, children suffering from eczema had an increased likelihood of snoring [with an OR of 1.80 (95% CI 1.28-2.54)], as well as of obstructive sleep apnea (OSA) [with a hazard ratio, HR, of 1.86 (95% CI 1.43-2.42)][2].

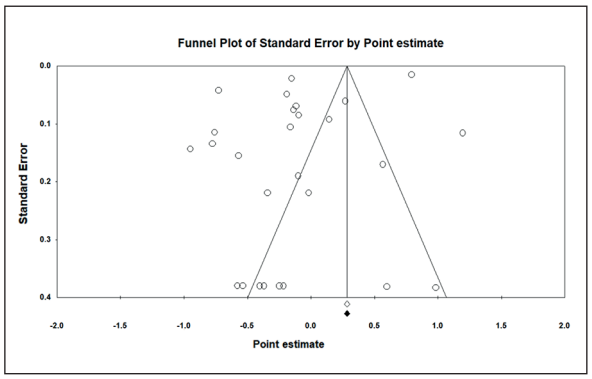

Figure 2. Funnel plot of the odds-ratios for all sleep-related adverse drug reaction-Dupilumab associations, showing no evidence of reporting bias.

On the one hand, as previously said, the relationship between sleep disorders and other cutaneous diseases, with defects at the level of the skin barrier, is complex and biunivocal. Adults suffering from OSA, especially if males and young (up to 34 years of age), are more likely to report atopic dermatitis [with a HR of 1.5 (95% CI 1.15-1.95)][2].

Dupilumab appears to be effective in improving the burden imposed by sleep disorders. Sleep-related ADRs appear to be rare, with only generic sleep disturbances/complaints and nocturnal dyspnea being statistically linked with the administration of the drug, probably suggesting that Dupilumab may not improve sleep quality in all patients and warranting a personalized treatment/management of the patient with atopy. Insomnia, which appears to be relevant in patients with atopic dermatitis, was not statistically significant in our investigation, with middle insomnia being, instead, statistically significant.

These findings are in line with published studies. For instance, Milanesi et al[17] have conducted a retrospective, multicenter study, recruiting a total of 36 patients (15 females and 21 males) aged 42.5 ± 14.3 years. Authors were able to detect an improvement in the "Pittsburgh Sleep Quality Index" (PSQI) at week 16, but

no significant further improvement at week 32 week, with 54% of the patients with a baseline elevated PSQI experiencing enhanced sleep quality during treatment.

Beck and colleagues[18] have recently reviewed findings from five randomized, double-blind, placebo-controlled clinical trials, namely the SOLO-1, the SOLO-2, the CAFÉ and the CHRONOS trials. All trials consistently showed sleep improvement at 16 weeks, with improvement at week 52 being observed only in some trials but not in all of them.

It has been hypothesized that Dupilumab could improve sleep in atopic dermatitis by different mechanisms: i) reducing itch, pain and responsiveness to pruritogens, which interfere with sleep and impact sleep quality; ii) *via* inhibition of IL-4 and IL-13 signaling pathways; and iii) *via* modulation of the circadian rhythm finely tuning endogenous cortisol production and release[2].

Future research should focus on the determinants of Dupilumab failure in improving/enhancing sleep quality and on the possible options that can be adopted to counteract/mitigate such effects, in such a way to design a tailored approach meeting the individual needs of the patient with atopy.

This study has some strengths, including the reporting of various disproportionality measures that allows a detailed assessment of the drug-ADR pairwise association. However, despite being comprehensive, the present analysis has some weaknesses. Limitations include: the heterogeneous nature of the database sources, which could also explain the lack of statistical significance for many sleep-related ADRs. Moreover, a direct causal relationship cannot be inferred from the current investigation and warrants further *ad hoc* epidemiological surveys (especially longitudinal ones) and careful clinical assessment for a proper identification and interpretation of the pharmacovigilance alert signals. Furthermore, the limitations of spontaneous reporting systems, including underreporting and reporting bias, merit consideration, and further research is needed, even though visual inspection of the funnel plot could not identify any bias.

Conclusions

In the present study, by means of a big data and machine learning analysis, we could support the statement that Dupilumab is usually effective in improving sleep quality and sleep disturbances/impairments, given the lack of statistical significance for most sleep-related ADRs. Further work is needed to closely scrutinize the impact of Dupilumab on sleep, in terms of underlying mechanisms, and to better understand residual sleep disorders in patients with atopic dermatitis and other allergic diseases treated with Dupilumab. Thus, sleep monitoring may be helpful for dermatologists in managing atopic dermatitis patients treated with dupilumab. With the future increase of targeted therapies (i.e., JAK and IL-13 inhibitors) and nano(bio)technological drugs, precision medicine, and in particular precision dermatology, is becoming more and more a reality, rather than being just a promise or a hope, and may help physicians identifying the best treatment approach in line with the patient's biological signature. However, as previously mentioned, the limitations of spontaneous reporting systems including underreporting and reporting bias, heterogeneity of sources and impossibility to infer any causal relationship merit consideration, and further research is needed.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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